REMARKS/ARGUMENTS

In response to the Office Action of August 30, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 39, 40 and 44 have been amended. Claims 2-38 were cancelled in a previous response (filed on November 3, 2003). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the claims made herein.

Claims 39 and 44 have been amended to remove the term "isolated".

Claim 40 has been amended to provide proper antecedent basis to the term "sample" in parent claim 39.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NO:1 a search of these claims would encompass this specific sequence. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker of SEQ ID NO:1 is found to be novel, methods and kits limited to its use should also be found novel.

Rejection under 35 USC 101

Claim 1, as presented on May 4, 2005, remains rejected under 35 USC 101 because the claimed invention allegedly has no apparent or disclosed specific and substantial credible utility.

The Examiner states that there is no argument that the role of the complement system is well described in the art. Moreover, the Examiner notes that the art teaches that complement C3 precursor protein could be potentially associated with Alzheimer's disease. However, the Examiner continues to assert that the issue at hand remains that the instant specification fails to provide any evidence of record or rely on any prior art disclosure to support the assertion that the claimed fragment 2-14 of SEQ ID NO:1 is useful for diagnosis or treatment of Alzheimer's disease.

Applicants respectfully submit that the Examiner's statements are contradictory and reveal an incomplete understanding of the invention described in the instant application. The Examiner acknowledges that the prior art teaches that complement C3 precursor protein could be associated with Alzheimer's disease but at the same time asserts that the instant specification fails to rely on any prior art disclosure to support the assertion that the claimed fragment of SEQ ID NO:1 is useful for diagnosis or treatment of Alzheimer's disease. Both of these assertions cannot be simultaneously true, as either supporting prior art exists or does not, thus, the Examiner's statements are contradictory.

It is well known that pathological changes in an organism can be reflected by changes in the serum protein pattern. A diagnosis may be predicted based upon the similarity of an unknown sample

pattern to a known pattern. Serum protein patterns are established by mass spectrometry.

Proteins, as collected from a serum sample, are too large to be effectively resolved by mass spectrometry and thus, are first subjected to separation by polyacrylamide gel electrophoresis. The resulting protein bands in the polyacrylamide gel which are deemed to be different between two comparable states are excised from the gel and subjected to further fragmentation by enzymes. These resulting peptides are then collected and purified by chromatography prior to identification using mass spectrometry. The peptides undergo step-wise degradation into sequence-defining fragments, i.e. the peptides are part of the original protein found in the serum sample. The resulting mass spectral profile is composed of parts of the original protein. See page 38, line 6 to page 40, line 12 of the instant specification.

The claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) was isolated by carrying out the methods of the invention and matches to a portion of the original protein, complement C3 precursor, found in the patient serum sample. Accordingly, the prior art (see, for example, references 2, 4 and 8 as cited in the response filed on May 4, 2005) is not required to teach the specifically claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) in order to be applicable since the claimed peptide is

representative of the complement C3 precursor protein present in the patient serum sample. Thus, contrary to the Examiner's assertion, the prior art does support Applicants' assertion of the usefulness of the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1)for diagnosis and/or treatment of Alzheimer's disease.

Applicants submit that Figures 1 and 2, as originally filed, are "evidence of record" which supports Applicants' assertion of the usefulness of the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) for diagnosis and/or treatment of Alzheimer's disease. Figure 2 shows a mass spectral profile obtained from Band 1 of the gel shown in Figure 1. Figure 2 also lists the ions identified from Band 1, including the claimed SEQ ID NO:1; an ion of complement C3 precursor protein weighing about 1682 daltons. Expression of the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) was shown, in Figure 1, to be decreased in Alzheimer's disease patients versus age-matched control patients, and thus, the claimed peptide is differentially expressed in Alzheimer's disease versus age-matched controls. This phenomenon is also explained at numerous points in previous responses (see, for example, page 28 of the response filed on May 4, 2005 and page 14 of the response filed on November 24, 2004).

In order to further illustrate this point, Applicants provide the attached Declaration (and figure) under 37 CFR 1.132. The

figure attached to the declaration is entitled "DEAE 3(Elution) AD vs. Age Matched AD (Control)" and represents Figure 1 as originally filed. This figure was produced by scanning the original photograph of the gel. Increased expression of Band C1(lanes 5-8, especially lane 5, all samples obtained from patients age-matched to the Alzheimer's disease patients) versus Band C2(lanes 1-4, especially lane 1, all samples obtained from Alzheimer's disease patients) is evident in the figure. Thus, decreased expression of the claimed peptide in Alzheimer's disease is also clearly shown. No new matter has been added; this figure is simply a clearer copy of Figure 1 as originally filed and is provided to clarify the presence and differential expression of the claimed biopolymer marker (amino acid residues 2-14 of SEQ ID NO:1). The gel shown in the figure does not represent new experimentation; the figure shows a clearer image of the original gel made at the time that the experiments described in the instant specification were first carried out.

The Examiner asserts that as it was fully explained in the previous communication of record, a proper biological marker is not the one that is "identified in a body fluid sample from an Alzheimer's patient" but rather the one that is also not found in a body fluid sample from a control patient free of Alzheimer's disease as well as from a patient suffering from another, not Alzheimer's disease.

Applicants respectfully submit that although the instant specification defines how Applicants intend for the term "biopolymer marker" to be interpreted (see page 5, lines 12-20 and page 11, lines 9-20); the Examiner continues to apply her own narrow definition without citing any reference to support that such a definition is "art-accepted".

First, the Examiner is reminded that Applicants are permitted to be their own lexicographer. They can define in the claims what they regard as their invention essentially in whatever terms they choose so long as the terms are not used in ways that are contrary to accepted meanings in the art (see MPEP 2173.01).

Applicants do not intend for the term "biopolymer marker" to be limited to expression in a disease and absence in normal, any differential expression can link a peptide/protein to a disease state (see page 5, lines 12-20 and page 11, lines 9-20 of the instant specification); for example, the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) is termed a "biopolymer marker" because while it is found in both disease and normal, expression is decreased in disease.

Applicants respectfully submit that such a definition for the term "biopolymer marker" is acceptable in the art. For example, Cheng et al. (see attached abstract, Journal of Neural Transmission 103 (4):433-446 1996; reference 1) identify homovanillic acid as

a useful marker for early diagnosis of Parkinson's disease since when comparing the levels of homovanillic acid in cerebrospinal fluid, they found a lower level in Parkinson's disease patients as compared with the levels found in age-matched controls.

Additionally, the Examiner makes several statements that one of ordinary skill in the art would not deem differential expression of the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) to be sufficient to term the peptide a "marker". For example, One skilled in the art readily appreciates that serum samples contain a plurality of proteins and the isolation of one of these proteins cannot alone serve as demonstration of finding a marker for Alzheimer's disease. And, a skilled artisan can reasonably conclude that the instant claimed peptide "appears to be down-regulated in Alzheimer's disease"; however, this alone is clearly not sufficient to assign a role of a marker or a tool for treatment of Alzheimer's disease for the claimed peptide.

Apparently, this is simply an opinion since the Examiner fails to support her statements by explaining **why** a person of ordinary skill in the art would doubt the usefulness of the claimed marker. The Examiner is reminded that it is improper to merely question operability-factual reasons must be set forth which would lead one of skill in the art to question the objective truth of the statement of operability (see MPEP 2107.02 IV).

Regardless, Applicants respectfully submit that one of ordinary skill in the art would **not** doubt the veracity of Applicants asserted use for the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1); since situations similar to the situation in the instant case have occurred in the prior art wherein a marker was recognized to have practical utility based upon differences in expression in a disease state versus expression in a normal physiological state.

For example, Andreasen et al. disclose a study wherein the differences in concentration of β-amyloid (1-42 aa) in cerebrospinal fluid between early- and late-onset Alzheimer's disease was evaluated. Andreasen et al. found that levels of CSF-β-amyloid were decreased in patients with Alzheimer's disease compared with controls and from these findings suggested that CSF-β-amyloid analyses may be of value in the clinical diagnosis of Alzheimer's disease, especially in the early course of the disease, when drug therapy may have the greatest potential of being effective but clinical diagnosis is particularly difficult (see attached abstract of Andreasen et al. Archives of Neurology 56(6):673-680 1999; reference 2).

Since the data of Andreasen et al. was available in the art at the time of the invention, one of skill in the art would be familiar with such practice (suggestion of a differentially

expressed peptide for diagnostics) and thus likely to find that linking the observed differential expression of the claimed biopolymer marker (amino acid residues 2-14 of SEQ ID NO:1)) to the suggested use of diagnostics and/or therapeutics of Alzheimer's disease is plausible.

Furthermore, it has been settled that an applicant is not required to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt". Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true (see MPEP 2164.07 I C).

Figure 1 establishes that the claimed biopolymer marker (amino acid residues 2-14 of SEQ ID NO:1) is differentially expressed between Alzheimer's disease patients and patients age-matched with the Alzheimer's disease patients. As pointed out above, one of skill in the art would recognize differentially expressed peptides to be potential markers for a disease condition. Thus, differential expression of a peptide between a disease state and a normal state is enough information to label a peptide a "marker" for the disease condition, no additional validation, comparison with other diseases, or further research is necessary.

Accordingly, Applicants respectfully contend that one of skill in the art would believe, based upon the information in the

specification in light of the knowledge in the prior art, that the claimed biopolymer marker (amino acid residues 2-14 of SEQ ID NO:1) is more likely than not to be a marker of Alzheimer's disease.

The Examiner continues to insist that the state of the art remains clear and sound that the definitive diagnosis of Alzheimer's disease could only be made during postmortem examination of the patient's brain.

Apparently, the Examiner believes that anything beyond the "status quo" in Alzheimer's research is considered to be of no value.

The Examiner is reminded that the purpose of the patent system is to promote the progress of science and the useful arts (see "Introduction" of the MPEP and Article 1, section 8 of the US Constitution). Applicants respectfully submit that dismissal of an invention as "useless" simply because it has never been done before does not promote the progress of science and may discourage further medical research. The progress of science usually occurs in a "piecemeal" fashion; meaning that a "discovery" does not arise by itself but often proceeds through multiple "discoveries". For example, a new Alzheimer's drug is a "discovery" while peptide markers, such as the instant invention are smaller "discoveries". These smaller "discoveries" , such as the instant invention, should be allowed patent protection because they promote the progress of

science by leading to further, larger "discoveries".

The decision in *In re Brana* (34 USPQ2d 1436 and MPEP 2107.01 III) lends support to this argument as well since the Federal Circuit stated that usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Patel (see Journal of Geriatric Psychiatry and Neurology 8:81-95 1995; reference 3) presents an overview of the experimental drug therapy of the cognitive impairment in Alzheimer's disease as the field was in the early 1990's. Applicants contend that Patel teaches that there are valid means for diagnostics of Alzheimer's disease other than post-mortem examination. Patel states at page 82, at the top of the left column:

"Over the years, many sets of diagnostic criteria for the clinical diagnosis of AD have been developed and refined, with the result that the diagnostic accuracy of AD has increased significantly. Today, the two most widely used clinical diagnostic criteria are those developed by NINCDS-ADRDA Work Group and the DSM III-R Work Group."

Thus, for at least fifteen years many methods other than post-mortem examination for diagnosing AD have been practiced and regarded as valuable. Accordingly, the Examiner's assertion regarding the state of the art in Alzheimer's research is of no consequence when considering the utility of the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) since it cannot be said that diagnostic methods other than postmortem examination have no value when the prior art demonstrates that this is simply not the case.

The Examiner asserts that Applicants' asserted utility for the claimed protein (amino acid residues 2-14 of SEQ ID NO:1) constitutes a utility that requires further research to identify or reasonably confirm a "real-world" context of use (see *Brenner v. Manson* 148 USPQ 689). While an assay that detects the presence of an agent that has a stated correlation to the onset of a specific disease condition would be considered a "substantial

utility" in the context of identifying potential candidates for preventive measures, in the instant case, the claimed peptide is suitable only for additional research.

An assessment that focuses on whether an invention is useful only in a research setting does not address whether the invention is in fact "useful" in a patent sense. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g. they are useful in analyzing compounds). See MPEP 2107.01

The identification of a protein/peptide showing decreased expression in Alzheimer's disease relative to expression in an age-matched control population puts a researcher one step closer to understanding the pathogenesis of Alzheimer's disease and thus, also one step closer to improved diagnosis and treatment of Alzheimer's disease. There is no question that improved diagnosis and treatment of Alzheimer's disease provides a tangible benefit to society; especially for the elderly population susceptible to the development of Alzheimer's disease. Thus, the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1) has a "real-world" use as is, in its currently available form.

In conclusion, based upon all of the above arguments (and those presented in previous responses), Applicants respectfully submit that one of ordinary skill in the art would immediately

appreciate why Applicants regard the claimed biopolymer marker (amino acid residues 2-14 of SEQ ID NO:1) as useful.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on May 4, 2005, stands rejected under 35 USC 112, first paragraph. Specifically, the Examiner asserts that since the claimed invention is not supported by either a clear asserted utility or a well established utility, one skilled in the art would clearly not know how to use the claimed invention.

Applicants respectfully disagree with the Examiner's assertions.

It has been established by prior arguments in the instant response that the claimed invention has both a clear asserted utility and a well established utility. Applicants assert that one of skill in the art would know how to use the claimed biopolymer marker (amino acid residues 2-14 of SEQ ID NO:1) as a marker for Alzheimer's disease. Therefore, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn as it was a consequence of the finding of a lack of utility which has now been rebutted.

CONCLUSION

In light of the foregoing remarks and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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